

# **Exhibit 2**



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>C12N 1/20, A61K 38/14, A01N 37/18</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/13053</b>  <b>(43) International Publication Date:</b> 18 March 1999 (18.03.99)
<b>(21) International Application Number:</b> PCT/US98/18701  <b>(22) International Filing Date:</b> 9 September 1998 (09.09.98)  <b>(30) Priority Data:</b> 08/926,636 10 September 1997 (10.09.97) US 09/149,832 8 September 1998 (08.09.98) US  <b>(71) Applicants:</b> VION PHARMACEUTICALS, INC. [US/US]; Four Science Park, New Haven, CT 06511 (US). YALE UNIVERSITY [US/US]; 451 College Street, New Haven, CT 06520 (US).  <b>(72) Inventors:</b> BERMUDEZ, David; 524 N. Main Street, Walling- ford, CT 06492 (US). LOW, Kenneth, B.; 1211 West Lake Avenue, Guilford, CT 06437 (US). ITTENSohn, Martina; 320 Willow Street, New Haven, CT 06511 (US).  <b>(74) Agents:</b> BALDWIN, Geraldine, F. et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>

**(54) Title:** GENETICALLY MODIFIED TUMOR-TARGETED BACTERIA WITH REDUCED VIRULENCE**(57) Abstract**

The present invention is directed to mutant *Salmonella* sp. having a genetically modified *msbB* gene in which the mutant *Salmonella* is capable of targeting solid tumors. The invention is also directed to *Salmonella* sp. containing a genetically modified *msbB* gene as well as a genetic modification in a biosynthetic pathway gene such as the *purI* gene. The present invention further relates to the therapeutic use of the mutant *Salmonella* for growth inhibition and/or reduction in volume of solid tumors.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/18701

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C12N 1/20; A61K 38/14; A01N 37/18

US CL : 435/252.8; 530/322; 514/2+

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/252.8; 530/322; 514/2+

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, MEDLINE, CAPLUS, STN

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	WO 97/18837 A1 (UNIVERSITY OF MARYLAND AT BALTIMORE), 29 May 1997, see pages 24, 25 and entire document.	1, 3-14, 31 ----- 17-27, 29, 30, 32, 36, 37.
X - Y	PAWELEK et al. Tumor-targeted Salmonella as A Novel Anti-melanoma Vector. Melanoma Research, 4th World Conference on Melanoma, Sydney, Australia. 10-14 June 1996, Vol. 7, (Suppl. 1), S141, see entire abstract.	15, 16, 28 ----- 17-27, 29, 30, 32

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	*A* document member of the same patent family

Date of the actual completion of the international search

05 NOVEMBER 1998

Date of mailing of the international search report

21 December 1998

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PATEL COOPERATION TREATY

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From the INTERNATIONAL BUREAU

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O.K. for filing

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**NOTICE INFORMING THE APPLICANT OF THE  
COMMUNICATION OF THE INTERNATIONAL  
APPLICATION TO THE DESIGNATED OFFICES**

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 18 March 1999 (18.03.99)		<b>IMPORTANT NOTICE</b>	
Applicant's or agent's file reference 8002-042-228			
International application No. PCT/US98/18701	International filing date (day/month/year) 09 September 1998 (09.09.98)	Priority date (day/month/year) 10 September 1997 (10.09.97)	
Applicant VION PHARMACEUTICALS, INC. et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:  
**AU,BR,CN,EP,IL,JP,KP,KR**

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

**AL,AM,AP,AT,AZ,BA,BB,BG,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,GH,GM,HR,HU,ID,IS,  
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SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW**

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on  
18 March 1999 (18.03.99) under No. WO 99/13053

**REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)**

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

**REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))**

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

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